swings in lung function, established or novel interventions to prevent decline could be implemented. Several clinical measures track disease progression, including FEV_1, body mass index (BMI) and pulmonary exacerbations (PE). Presently, intervention is driven by lagging indications of lung function decline, which is far less beneficial than intervening in at risk subpopulations before decline is manifest. Therefore, methods that can be used to predict CF disease progression are highly desirable, as they would preemptively identify those at risk of future disease progression, allowing caregivers to tailor treatments and select intervention to prevent pulmonary decline. Personalizing therapy is a critical need in CF, as broad application of all available therapies leads to a high daily treatment burden and poor adherence. These measures are lagging indicators of disease progression that result from molecular changes directly or indirectly related to CFTR dysfunction. Furthermore, current monitoring of lung function data is inadequate, and fails to utilize novel biostatistical tools to identify patients at risk for future decline. The disclosed methods address one or more of aforementioned needs in the art.

BRIEF SUMMARY

[0007] Disclosed herein are methods for treating an individual at risk for non-linear lung function decline. The methods, in certain aspects, include the steps of a) determining one or more covariates associated with lung function in said individual, said covariate being selected from one or more of a clinical measure, a biomarker or an imaging marker; b) calculating a risk probability score based on said determining of one or more covariate, said risk probability score being used to characterize an individual as having no predicted lung impairment, mild predicted lung impairment, moderate predicted lung impairment, or severe predicted lung impairment; and c) treating said individual characterized as having mild predicted lung impairment, moderate predicted lung impairment, or severe predicted lung impairment with one or more of increased frequency of disease monitoring, increased frequency of infection monitoring, an anti-inflammatory therapy, or combinations thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

[0008] This application file may contain at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

[0009] Those of skill in the art will understand that the drawings, described below, are for illustrative purposes only. The drawings are not intended to limit the scope of the present teachings in any way.

[0010] FIG. 1. Lung function in a typical CF patient. Lung function is separated into stages, with a stable period (light grey), an erratic period with large swings in FEV_1 (dark grey), and a decline stage (black).

[0011] FIG. 2. Disease progression in CF. In depth serum proteomic analysis can capture molecular changes in serum that give rise to downstream organ pathology.

[0012] FIG. 3. Lung function decline with age. Comparison from data compiled from 1990-2014. Despite improvement in lunch function at early age, the rate of decline is unaffected by modern therapies. Source: CF Foundation Patient Registry data.

[0013] FIG. 4. Box plots of CF disease severity serum biomarkers. Example of differential expression identified serum biomarkers of lung disease severity. Forty-four candidates whose quantities differ by 0.35-5.4-fold between mild and severe disease have been identified.

[0014] FIG. 5. Functional Data (FD) analysis model is superior to presently available models of lung function decline. CFF PR analyses with point estimates from FD analysis (solid line), cubic (dashed line), quadratic (dotted line) and conventional linear (dot-dash line) mixed models of decline (A) and rate of decline (B); stratified by birth cohorts born before 1981 (solid line), 1981-1988 (dashed line), 1989-1994 (dot-dash line), and after 1994 (dotted line) (C); stratified by survival (solid line) and death (dashed line) for patients less than 19 years of age (D). The FD model in (A) reflected the dynamic status of lung function during young adolescence/early adulthood; traditional models found no changes and even indicated gains in lung function (e.g. cubic). The arrow at the "dip" in (B) shows 1) Patients attained most rapid decline at median age (IQR) 16.3 (13.5, 21.0) years; 2) Degree of maximal $FEV_1\%$ loss was variable (mean: 1.98% pred/yr, 95% CI: 1.86, 2.10). Longitudinal $FEV_1\%$ measures shared correlation for up to 9 years, highlighting the potential of short-term clinical interventions to impact long-term lung function. Further subgroup analysis revealed that $FEV_1\%$ curves vary according to survivorship and birth cohort (C-D), highlighting left- and right-truncation biases, respectively.

[0015] FIG. 6. Biomarker correlation with functional principle component (FPCA) analysis of lung function. Examples shown for 4 of 18 biomarkers discovered in preliminary cross-sectional proteomic analyses that significantly correlate with FPCA analysis of FEV_1. The first principle component score (FPC1, y-axis); the thick dashed black line is the fit to the data using a scatterplot smoother; positive association (r) indicates that higher values of these markers may lead to worsening FEV_1 trajectory, while negative associates (−4) indicates that higher values of these markers correspond to improvements in the FEV_1 trajectory. Although these studies were conducted in discovery mode to capture the maximal number of biomarkers, data on individual markers may be improved under targeted MS and ELISA analyses.

[0016] FIG. 7. On the left, smoothed FEV_1 observed over age (in years) for the EPIC cohort. On the right, the corresponding rate of change in FEV_1 (expressed as % predicted/year) over age.

[0017] FIG. 8. Schematic of biomarker integrated dynamic modelling of FEV_1. On the left, the full model space for all CF patients and possible covariates; the large circle is the space for the full dynamic prediction model, and the star denotes the true associates between each CFFPR/EPIC covariate and rapid (non-linear) decline. On the bottom right, the bottom circle is the space for the external data model that is fit to the CFFPR; the bottom star marks the parameters Θ^* that would minimize the mathematical distance between the full model with all covariates and the model with only the CFFPR covariates. On the upper right, the circle shows a star being mapped to the same space as the external model, in order to perform model calibration and obtain more efficient, unbiased estimates.

[0018] FIG. 9. Dynamic prediction modeling. Dynamic predictions for female (left column) and male (right column) CF patients. In the left column, the female patient had data